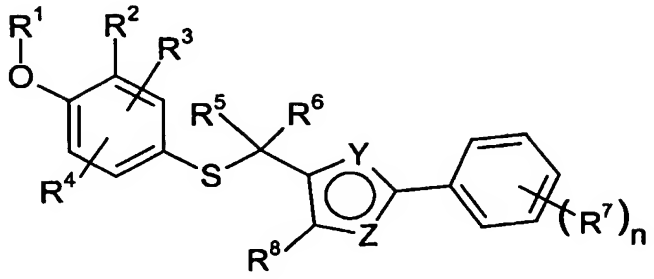
Claims

We claim:

1. A process for the preparation of a compound of formula (IV),



(IV)

wherein,

R^1 is selected from the group consisting of H, $-Si(R^9)_3$, $-C(R^{10}R^{10})C(O)_2H$, benzyl, allyl, and C_{1-6}alkyl;

R^2, R^3, and R^4 are independently selected from the group consisting of H, C_{1-3}alkyl, $-OCH_3$, $-CF_3$, allyl, and halogen;

R^5 and R^6 are independently selected from the group consisting of H, phenyl, benzyl, C_{1-6}alkyl, and allyl;

each R^7 is independently $-CF_3$, C_{1-3}alkyl, $-OCH_3$, or halogen;

R^8 is selected from the group consisting of H, $-CF_3$, and C_{1-6}alkyl;

one of Y and Z is N and the other is S or O;

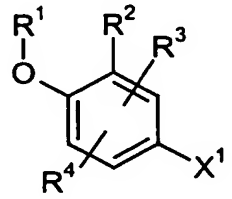
each R^9 is independently C_{1-6}alkyl, or arylC_{1-6}alkyl, or two R^9 groups together with the silicon atom to which they are attached form a 5-7 membered ring;

each R^{10} is independently H or C_{1-3}alkyl, or both R^{10} groups together with the carbon atom to which they are attached form a 3-6 membered ring; and

n = 0, 1, 2, 3, 4, or 5;

said method comprising the steps of:

a) treating of a compound of formula (I) with an alkyl lithium reagent, magnesium (0), or magnesium (0) followed by treating with a dihalo zinc (II) reagent,



(I)

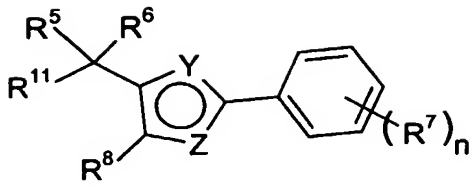
wherein,

R^1, R^2, R^3, and R^4 are as defined above; and

X^1 is selected from the group consisting of Cl, Br, and I;

b) followed by treating with sulfur; and

c) followed by treating with a compound of formula (III),



(III)

wherein,

R^5, R^6, R^7, R^8, Y, Z, and n are as defined above;

R^{11} is Cl, Br, I, or $-OS(O)_2R^{12}$; and

R^{12} is selected from the group consisting of C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, and $-CF_3$.

2. A process according to Claim 1, wherein said process is performed without isolation of intermediate compounds between steps (a) and (b) or (b) and (c).

3. A process according to either one of Claims 1 or 2, wherein R^1 is $-Si(R^9)_3$.

4. A process according to either one of Claims 1 or 2, wherein R^1 is $-Si(CH_3)_2t$-Bu.

5. A process according to either one of Claims 1 or 2, wherein R^1 is $-C(R^{10}R^{10})C(O)_2H$.

6. A process according to Claim 5, wherein R^{10} is $-CH_3$.

7. A process according to either one of Claims 1 or 2, wherein R^{11} is Cl or $-OS(O)_2R^{12}$, and R^{12} is C_{1-6}alkyl.

8. A process according to either one of Claims 1 or 2, wherein:

R^1 is -Si(CH_3)$_2$*t*-Bu;

R^2 is –CH_3;

R^3 and R^4 are H;

R^5 and R^6 are H;

n is 2;

one R^7 is fluorine in the *ortho* position and the other is –CF_3 is the *para* position;

R^8 is –CH_3;

Y is S; and

Z is N.

9. A process according to either one of Claims 1 or 2, wherein:

R^1 is -C($R^{10}R^{10}$)C(O)$_2$H;

R^2 is –CH_3;

R^3 and R^4 are H;

R^5 and R^6 are H;

n is 2;

one R^7 is fluorine in the *ortho* position and the other is –CF_3 is the *para* position;

R^8 is $-CH_3$;

Y is S;

Z is N; and

each R^{10} is $-CH_3$.

10. A process according to Claim 8, said process further comprising the step cleaving the R^1 silyl group, to afford a compound of formula (IV), wherein R^1 is –H.

11. A process according to Claim 8, said process further comprising the steps of:

d) cleaving the R^1 silyl group to afford a compound of formula (IV), wherein R^1 is –H; and

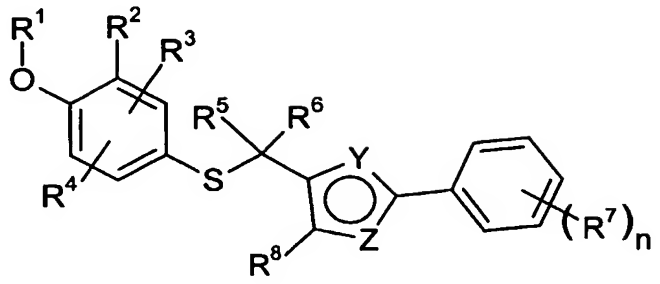
e) treating with an alkylating agent to afford a compound of formula (IV), wherein R^1 is $-C(R^{10}R^{10})C(O)_2H$, and R^{10} is $-CH_3$.

12. A process according to Claim 8, said process further comprising the steps of

d) cleaving the R^1 silyl group to afford a compound of formula (IV), wherein R^1 is –H ; and

e) treating with 1,1,1-trichloro-2-methylpropan-2-ol, to afford a compound of formula (IV), wherein R^1 is $-C(R^{10}R^{10})C(O)_2H$, and R^{10} is $-CH_3$.

13. A compound of formula (IV),



(IV)

wherein:

R^1 is --Si(R^9)$_3$;

R^2, R^3, and R^4 are independently selected from the group consisting of H, C_{1-3}alkyl, -OCH_3, -CF_3, allyl, and halogen;

R^5 and R^6 are independently selected from the group consisting of H, phenyl, benzyl, C_{1-6}alkyl, and allyl;

each R^7 is independently selected from –CF_3, C_{1-3}alkyl, -OCH_3, or halogen;

R^8 is selected from the group consisting of H, -CF_3, and C_{1-6}alkyl;

one of Y and Z is N and the other is S or O;

each R^9 is independently selected from C_{1-6}alkyl, arylC_{1-6}alkyl, or two R^9 groups together with the silicon atom to which they are attached form a 5-7 membered ring; and

n = 0, 1, 2, 3, 4, or 5.

14. A compound according to Claim 13, wherein:

R^1 is $-Si(R^9)_3$;

R^2 is $-CH_3$;

R^3, R^4, R^5, and R^6 are hydrogen;

n is 2;

one R^7 is F in the *ortho* position and the other is $-CF_3$ in the *para* position;

R^8 is $-CH_3$;

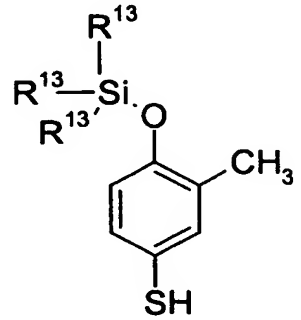
R^9 is C_{1-6}alkyl;

Y is S; and

Z is N.

15. A compound according to either one of Claims 13 and 14, wherein R^1 is $-Si(CH_3)_2t$-Bu.

16. A compound of formula (V),



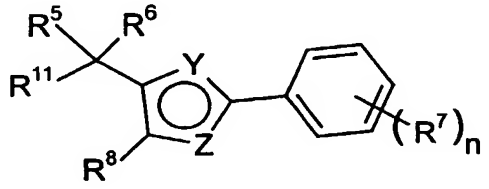
(V)

wherein:

R^{13} is C_{1-6}alkyl, C_{6-14}arylC_{1-6}alkyl, or C_{6-14}aryl.

17. A compound according to Claim 16, wherein two R^{13} are $-CH_3$ and the other is t-Bu.

18. In another aspect of the invention is featured a process for the preparation of compounds of formula (III),



(III)

wherein:

R^5 and R^6 are independently selected from the group consisting of H, phenyl, benzyl, C_{1-6}alkyl, and allyl;

each R^7 is independently selected from $-CF_3$, C_{1-3}alkyl, $-OCH_3$, or halogen;

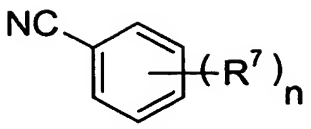
R^8 is H, $-CF_3$, or C_{1-6}alkyl;

one of Y and Z is N and the other is S or O;

R^{11} is –OH; and

n = 0, 1, 2, 3, 4, or 5;

said process comprising the step of treating a compound of formula (XVII) with thioacetic acid,



(XVII)

wherein:

each R^7 is independently selected from $-CF_3$, C_{1-3}alkyl, $-OCH_3$, or halogen;

and

n = 0, 1, 2, 3, 4, or 5.

19. A process according to Claim 18, wherein said process further comprises the step of treating with an α-halo-β-ketoester.

20. A process according to Claim 19, wherein said process further comprises the step of treating with a reducing agent.

21. A process according to any one of Claims 18-20, wherein R^5 and R^6 are hydrogen, n is 2, one R^7 is fluorine and the other is $-CF_3$, R^8 is C_{1-6}alkyl, Y is S, Z is N, and R^{11} is –OH.

22. A process according to any one of Claims 18-21, wherein one R^7 is fluorine in the *ortho* position and the other is $-CF_3$ in the *para* position, and R^8 is $-CH_3$.

23. A process according to either one of Claims 18-20, wherein the compound of formula (III) is {2-[2-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl}methanol.

24. A process according to any one of Claims 1-12, wherein said compound of formula (I) is treated with an alkyl lithium reagent.